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European Patent Office
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Germany

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your ref
our ref 61.78607/001

BY FACSIMILE
Confirmation by Mail

Dear Sirs

International Patent Application No. PCT/GB03/02942 of National Blood Authority et al

I write in reply to the first Written Opinion dated 30 March 2004.

The Written Opinion raised a lack of novelty objection against the product claims (claims 9-13), stating that they would not be admissible in the European Regional phase. The applicants will deal with any objections to these claims during the National/Regional phases of the application.

The Written Opinion raised a lack of inventive step objection against the method claims, claims 1-9. The applicants agree with the Examiner that the technical problem underlying the invention may be seen as the provision of an alternative method for producing a virus inactivated thrombin preparation. However, none of the prior art cited by the Examiner would have led a skilled person to the method of the present invention.

The present method comprises carrying out a solvent-detergent virus inactivation on a solution comprising prothrombin and factor X. The inactivated solution is then loaded onto an anion exchange medium which is washed to remove the reagents used for the solvent-detergent virus inactivation step. The prothrombin is then activated, whilst bound to the medium, by the addition of metal ions to form thrombin. The product thrombin may then be selectively eluted from the anion exchange medium.

As discussed on pages 2-3 of the present application, previous attempts to utilise solvent-detergent treated prothrombin to form thrombin required use of added phospholipids for the activation step. The present invention overcomes this defect in the prior art by carrying out the activation using only metal ions whilst the prothrombin is bound to the anion exchange medium. The present method is therefore a more efficient and convenient way to obtain highly purified virus inactivated thrombin than the prior art methods.

D1 (EP-A 0543178) discloses the activation of prothrombin complex to form thrombin in solution. The prothrombin complex used can be purified first on anion exchanges and then pasteurised to inactivate viruses (see page 2, lines 37-42). The activation is carried out by

addition of a salt with an anion which complexes calcium. A catalytic quantity of thrombin is also required for the activation step. Nowhere in D1 is there any suggestion that the activation of the prothrombin complex to form thrombin could occur whilst the prothrombin was bound to an anion exchange medium. Furthermore, there is no suggestion in D1 that the virus inactivation could take place by solvent-detergent treatment before binding of the prothrombin to an anion exchange resin.

The method of D1 requires use of thrombin itself for the activation (either endogenus thrombin or added thrombin). This leads to a potentially less-controllable and less-virus safe process than that now claimed, which requires activation only by addition of a metal ion. Furthermore, the pasteurisation described in D1 is a difficult process to control for labile proteins.

D2 (EP-A 0439156) discloses the activation of prothrombin in solution by addition of thromboplastin and calcium, followed by purification of the resultant thrombin by anion and cation exchange chromatography. There is no reference to any virus inactivation processes in D2. Nor is there any suggestion that the activation could take place whilst the prothrombin was bound to an anion exchange medium. Furthermore, the activation process requires thromboplastin which is itself a potential source of viral contamination.

D3 (EP-A 1136084) discloses the activation of prothrombin in solution to form thrombin. It is stated that the prothrombin can be purified on an ion exchanger and then subjected to virus inactivation by, for example, pasteurisation prior to activation to form thrombin. However, there is no suggestion in D3 that the virus inactivation could take place by solvent-detergent treatment of the prothrombin. Furthermore, there is no suggestion that the prothrombin could be activated to form thrombin whilst bound to an anion exchange resin.

D4 (WO 00/71153) simply discloses use of thrombin-fibrinogen kits as medicaments. There is reference to the thrombin being "virus inactivated" but no disclosure of how exactly it is prepared.

D7 (EP-A 1161958) discloses a method for the inactivation of viruses in biological liquids by solvent-detergent treatment. It does not disclose any method for the preparation of thrombin from prothrombin.

None of the prior art would have led a skilled person to the claimed process wherein thrombin is obtained from solvent-detergent treated prothrombin bound to an anion exchange medium. The method of the invention allows efficient preparation of virus-safe thrombin without the need for addition of thrombin or thromboplastin, which are themselves sources of potential viral contamination. The process of the present invention utilises metal ions to activate the prothrombin to form thrombin, allowing preparation of highly pure virus inactivated thrombin in a single step.

In the light of the above, it is hoped that the Examiner can now acknowledge an inventive step for claims 1-8 of the present application. It is therefore hoped that the Examiner can issue an International Preliminary Examination Report indicating an inventive step for at least claims 1-8 of the present application.

Please acknowledge receipt of this letter by returning the EPO form 1037 which accompanies the confirmation copy.

Yours faithfully
Frank B. Dehn & Co.

Annabel R. Beacham

enc.jg

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Einsender / Sender / Expéditeur:

Frank B. Dehn & Co.
179 Queen Victoria Street
London
EC4V 4EL
England

D-80298 München
(+49-89)2399-0
Tx 523 656 epmu d
Fax (+49-89)2399-44 65

P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
(+31-70) 340-2040
Tx 31 651 epo nl
Fax (+31-70)340-3016

D-10958 Berlin
(+49-30) 25901-0
Fax (+49-30) 25901-840

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1	PCT/GB03/02942	61.78607/001	Confirmation fax of 30 June 2004.
2			
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